PLEASE ENTER A COMMAND OR BE LOGGED OFF IN 5 MINUTES
? s bcl (w) 2 and (antisens? or ribozym?)

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          22482  BCL
        4665377  2
          19789  BCL(W)2
          29062  ANTISENS?
           5086  RIBOZYM?
     S1     665  BCL (W) 2 AND (ANTISENS? OR RIBOZYM?)
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? s s1 and py<1999

Processing

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            665  S1
       21626235  PY<1999
     S2     327  S1 AND PY<1999
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? rd

...examined 50 records (50)
...examined 50 records (100)
...examined 50 records (150)
...examined 50 records (200)
...examined 50 records (250)
...examined 50 records (300)
...completed examining records

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     S3     226  RD (unique items)
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? t s3/3,ab/all

3/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10722083 21032090
Enhancement of Vp16 inducing apoptosis of leukemic cells by retrovirus-mediated **bcl-2** anti-sense RNA]
Cao G; Wang S; Chen D
Central Laboratory, People's Hospital, Beijing Medical University, Beijing 100044.
Zhonghua xue ye xue za zhi (China) Sep **1998**, 19 (9) p467-9, ISSN 0253-2727 Journal Code: CNL
Languages: CHINESE
Document type: Journal Article
OBJECTIVE: To explore the effects of retrovirus-mediated **bcl-2 antisense** RNA on apoptosis of leukemic cells. METHODS: Retrovirus was packaged in vitro with PA317 cells and Jurkat cell was transducted with collected virus; The expressions of **bcl-2** mRNA and protein were assayed by RT-PCR and Western blotting, respectively. Apoptosis was assayed by flow cytometry and DNA "ladder". RESULTS: Expression of intrinsic **bcl-2** was decreased, and the sensitivity of leukemic cells to Vp16 and the apoptosis of leukemic cells line Jurkat cells were enhanced by transfected **bcl-2 antisense** RNA. CONCLUSION: **Antisense bcl-2** enhances Vp16 inducing apoptosis of leukemic cells. The results provide a useful experimental basis for leukemia therapy.

3/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10113430 98421812
Involvement of **Bcl-2** family and caspase-3-like protease in NO-mediated neuronal apoptosis.
Tamatani M; Ogawa S; Niitsu Y; Tohyama M
Department of Anatomy and Neuroscience, Osaka University Medical School, Suita, Japan.
Journal of neurochemistry (UNITED STATES) Oct **1998**, 71 (4) p1588-96, ISSN 0022-3042 Journal Code: JAV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
To clarify mechanisms of neuronal death in the postischemic brain, we examined whether astrocytes exposed to hypoxia/reoxygenation exert a neurotoxic effect, using a coculture system. Neurons cocultured with astrocytes subjected to hypoxia/reoxygenation underwent apoptotic cell death, the effect enhanced by a combination of interleukin-1beta with hypoxia. The synergistic neurotoxic activity of hypoxia and interleukin-1beta was dependent on de novo expression of inducible nitric oxide synthase (iNOS) and on nitric oxide (NO) production in astrocytes. Further analysis to determine the neurotoxic mechanism revealed decreased **Bcl-2** and increased Bax expression together with caspase-3 activation in cortical neurons cocultured with NO-producing astrocytes. Inhibition of NO production in astrocytes by N(G)-monomethyl-L-arginine, an inhibitor of NOS, significantly inhibited neuronal death together with changes in **Bcl-2** and Bax protein levels and in caspase-3-like activity. Moreover, treatment of neurons with a bax **antisense** oligonucleotide inhibited the caspase-3-like activation and neuronal death induced by an NO donor, sodium nitroprusside. These data suggest that NO produced by astrocytes after hypoxic insult induces apoptotic death of neurons through mechanisms involving the caspase-3 activation after down-regulation of **Bcl-2** and up-regulation of Bax protein levels.

3/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10105613 98288300
Cationic liposomes coated with polyethylene glycol as carriers for oligonucleotides.
Meyer O; Kirpotin D; Hong K; Sternberg B; Park JW; Woodle MC; Papahadjopoulos D
Department of Cellular and Molecular Pharmacology, University of California San Francisco, San Francisco, California 94143, USA.
Journal of biological chemistry (UNITED STATES) Jun 19 **1998**, 273 (25) p15621-7, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: P50CA58207, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Modification of liposome surface with polyethylene glycol was used to improve oligodeoxyribonucleotide (ODN) loading, stability of the resulting complexes, and specificity of cellular delivery of ODN by cationic liposomes. Liposomes composed of a cationic lipid (DOTAP, DOGS, DDAB), a neutral lipid (DOPE), and a phospholipid derivative of polyethylene glycol (PEG-PE) formed a complex with 18-mer phosphorothioate up to ODN/lipid molar ratio of 0.25. The complexes showed intact vesicular structures similar to original liposomes and their size (100-130 nm) was unchanged after several weeks of storage, whereas complexes lacking PEG-PE showed progressive aggregation and/or precipitation. After exposure to human plasma, PEG-modified cationic liposomes retained over 60% of the originally bound ODN. PEG-coated complexes resulted in 4-13-fold enhancement of the ODN uptake by human breast cancer cells in serum-supplemented growth medium, relative to free ODN. Complexes containing conjugated anti-HER2

F(ab') fragments at the [redacted]stal termini of PEG chains eff[redacted]ently delivered ODN primarily into the cytoplasm and nuclei of HER2 overexpressing cancer cells and greatly enhanced the biological activity of **antisense** ODN. The development of PEG-modified cationic liposomes may lead to improved ODN potency in vivo.

3/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10103577 98251288
The intracellular domain of p55 tumor necrosis factor receptor induces apoptosis which requires different caspases in naive and neuronal PC12 cells.
Haviv R; Stein R
Department of Neurobiochemistry, George S. Wise Faculty of Life Sciences, Tel-Aviv University, Ramat Aviv, Israel.
Journal of neuroscience research (UNITED STATES) May 15 **1998**, 52 (4) p380-9, ISSN 0360-4012 Journal Code: KAC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Apoptosis is induced in cells via distinct pathways, which may differ according to various stimuli and different cell types. One apoptotic stimulus is the activation of receptors such as the p55 tumor necrosis factor (TNF) receptor. These receptors transduce their apoptotic signals via a cytoplasmic region termed the death domain. Here we investigated the apoptotic pathway induced by overexpression of the intracellular domain of p55 TNF receptor (p55-IC) in a neuronal model system consisting of PC12 cells. Using the tetracycline-regulated transactivator system, which allows controlled gene expression, we show that overexpression of p55-IC induces apoptosis in both naive and neuronal PC12 cells. The apoptosis-inducing effect of p55-IC is blocked by the expression of **bcl-2**, suggesting that p55-IC induces apoptosis in PC12 cells via a pathway controlled by **bcl-2** . The need for caspases in the p55-IC-induced cell death effect in naive and neuronal PC12 cells was studied by examining the effects of broad-spectrum and specific inhibitors of caspases as well as expression of **antisense** caspase-2 RNA. The broad-spectrum caspase inhibitor benzyloxycarbonyl-Val-Ala-Asp-fluoromethyl -ketone blocked p55-IC-induced cell death in both naive and neuronal cells, suggesting that caspases are needed for this process in both cell types. Caspase-1-like proteases are most probably not involved in the process since neither expression of crmA nor treatment with the caspase-1-specific peptide inhibitor Ac-Try-Val-Ala-Asp-aldehyde had any protective effect. Interestingly, expression of **antisense** caspase-2 RNA blocked the p55-IC-induced cell death in naive but not in neuronal PC12 cells, whereas the caspase-3-like specific inhibitor Ac-Asp-Glu-Val-Asp-aldehyde partially inhibited this death in neuronal but not in naive cells. These results suggest that the apoptosis-inducing effect of p55-IC requires different caspases in naive and neuronal PC12 cells.

3/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10091523 98035198
Bcl-2 influences axonal growth rate in embryonic sensory neurons.
Hilton M; Middleton G; Davies AM
School of Biological and Medical Sciences, University of St. Andrews, Fife, UK.
Current biology (ENGLAND) Oct 1 **1997**, 7 (10) p798-800, ISSN 0960-9822 Journal Code: B44
Languages: ENGLISH

Document type: JOURNAL ARTICLE

Bcl-2 plays a key role in regulating cell survival in the immune and nervous systems. Mice lacking the **bcl-2** gene have markedly reduced numbers of B and T cells as a result of increased apoptosis, whereas mice with a transgene causing high levels of **Bcl-2** expression in the immune system show extended survival of B and T cells. Overexpression of **Bcl-2** in cultured neurons prevents their death following neurotrophin deprivation, and mice with a **bcl-2** transgene under the control of a neuron-specific enolase promoter have increased numbers of neurons in several regions. Cultured neurons expressing **antisense bcl-2** RNA have an attenuated survival response to neurotrophins, and neurons of postnatal **bcl-2** -deficient mice die more rapidly following NGF deprivation in vitro and are present in reduced numbers in vivo. Here, we show that **Bcl-2** also plays a role in regulating axonal growth rates in embryonic neurons. Sensory neurons from the trigeminal ganglia of **bcl-2** -deficient mouse embryos, removed from the embryo on embryonic day 11 or 12, extend axons more slowly in vitro than do neurons from wild-type embryos of the same age. Serial measurements of axonal length in the same neurons revealed that there were marked differences in axonal growth rate between **bcl-2**-deficient and wild-type neurons, irrespective of whether the neurons were grown with nerve growth factor, brain-derived neurotrophic factor or neurotrophin-3. Because there was no significant difference in the numbers of wild-type and **bcl-2**-deficient neurons surviving with each neurotrophin at this early stage of development, the effect of **Bcl-2** on axonal growth rate is not a consequence of its well documented role in preventing apoptosis.

3/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10090981 98025896

Cross-resistance of CD95- and drug-induced apoptosis as a consequence of deficient activation of caspases (ICE/Ced-3 proteases).

Los M; Herr I; Friesen C; Fulda S; Schulze-Osthoff K; Debatin KM
Hematology/Oncology, University Children's Hospital, Ulm, Germany.

Blood (UNITED STATES) Oct 15 **1997**, 90 (8) p3118-29, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The cytotoxic effect of anticancer drugs has been shown to involve induction of apoptosis. We report here that tumor cells resistant to CD95 (APO-1/Fas) -mediated apoptosis were cross-resistant to apoptosis-induced by anticancer drugs. Apoptosis induced in tumor cells by cytarabine, doxorubicin, and methotrexate required the activation of ICE/Ced-3 proteases (caspases), similarly to the CD95 system. After drug treatment, a strong increase of caspase activity was found that preceded cell death. Drug-induced activation of caspases was also found in ex vivo-derived T-cell leukemia cells. Resistance to cell death was conferred by a peptide caspase inhibitor and CrmA, a poxvirus-derived serpin. The peptide inhibitor was effective even if added several hours after drug treatment, indicating a direct involvement of caspases in the execution and not in the trigger phase of drug action. Drug-induced apoptosis was also strongly inhibited by **antisense** approaches targeting caspase-1 and -3, indicating that several members of this protease family were involved. CD95-resistant cell lines that failed to activate caspases upon CD95 triggering were cross-resistant to drug-mediated apoptosis. Our data strongly support the concept that sensitivity for drug-induced cell death depends on intact apoptosis pathways leading to activation of caspases. The identification of defects in caspase activation may provide molecular targets to overcome drug resistance in tumor cells.

3/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10090569 98018463
NSAID-induced apoptosis in Rous sarcoma virus-transformed chicken embryo fibroblasts is dependent on v-src and c-myc and is inhibited by **bcl-2**.
Lu X; Fairbairn DW; Bradshaw WS; O'Neill KL; Ewert DL; Simmons DL
Department of Zoology, Brigham Young University, Provo, UT 84602, USA.
Prostaglandins (UNITED STATES) Aug **1997**, 54 (2) p549-68, ISSN 0090-6980 Journal Code: Q76
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Mounting epidemiological and experimental evidence implicates non-steroidal antiinflammatory drugs as anti-tumorigenic agents. Our previous work showed that nonsteroidal antiinflammatory drug treatment of src-transformed chicken embryo fibroblasts caused apoptosis--a mechanism by which these drugs might exert their anti-tumorigenic effect. The present studies employ a sensitive technique for detecting single- and double-stranded DNA cleavage (the comet assay) to quantitate apoptosis. By this method pp60v-src, which antagonizes apoptosis in many cell systems, was found to induce apoptosis in 11-23% of serum-starved fibroblasts. However, treatment with diclofenac following pp60v-src activation produced a much stronger response beginning within 6 hours of treatment that resulted in 100% lethality. During cell death, cyclooxygenase-2 but not cyclooxygenase-1 mRNA was found to be uniformly increased by all apoptotic drugs tested. Examination of the expression of apoptosis-associated genes showed that c-rel and p53 (found in normal or v-src-transformed chicken embryo fibroblasts at moderate levels), and **bcl-2** (present at an extremely low level) were largely unchanged by treatment with eight different nonsteroidal antiinflammatory drugs. However, overexpression of human **bcl-2** inhibited diclofenac-mediated apoptosis by 90%, demonstrating directly that **bcl-2** expression can regulate nonsteroidal antiinflammatory drug induction of cell death. The proto-oncogene c-myc is known to cause apoptosis in chicken embryo fibroblasts when artificially overexpressed in cells deprived of trophic factors. We found that nonsteroidal antiinflammatory drug treatment following pp60v-src activation persistently induced myc protein and mRNA by more than 20-fold above that evoked by pp60v-src activation alone. Moreover, transfection of **antisense** c-myc oligonucleotides reduced drug-induced myc expression by 80% and caused a concomitant 50% reduction in cell death. These findings suggest that nonsteroidal antiinflammatory drug-induced apoptosis proceeds through a src/myc dependent pathway which is negatively regulated by **bcl-2**.

3/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10083848 97376497
Enhanced expression of **bcl-2** following **antisense** oligonucleotide mediated growth factor deprivation.
Rubenstein M; Chou P; Mirochnik Y; Guinan P
Hektoen Institute for Medical Research, Department of Urology, Rush Presbyterian St Lukes Medical Center, Chicago, Illinois 60612, USA.
Medical oncology (ENGLAND) Mar **1997**, 14 (1) p23-9, ISSN 1357-0560 Journal Code: B3A
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Although the role of **bcl-2** in apoptosis has been described, its involvement in prostate cancer (CAP) progression is less well understood, but thought to be involved with the transition of CAP from androgen-sensitivity to androgen-independence, where its expression is

augmented following a[redacted]ogen ablation. For treating [redacted]hese recurrent androgen-independent tumors, following hormone treatment failure, a new tier of therapy based upon growth factor deprivation has been suggested, implemented by **antisense** oligonucleotides (oligos) directed against mRNA encoding a critical growth regulatory autocrine loop (comprised of transforming growth factor-alpha (TGF-alpha) and its binding site, the epidermal growth factor receptor (EGFR). To determine whether oligo-induced growth factor deprivation therapy similarly enhanced expression of **bcl-2** (as follows androgen deprivation) human prostate cancer derived PC-3 cells were treated in vitro with oligos directed against TGF-alpha (MR-1) and/or EGFR (MR-2). After 5 days of treatment cells were immunochemically stained for human **bcl-2** . In similar experiments, cells were treated for 3 days prior to extraction of proteins, Western blot analysis, photography and computer evaluation of protein density by SigmaScan software. Immunostained cells treated with oligos directed against mRNA encoding TGF-alpha (MR-1) either alone or in combination with that directed against EGFR (MR-2) had increased **bcl-2** expression (+3 to +5). In addition, the intensity of Western blots scanned for **bcl-2** expression were 19%, 32% and 30% greater in cells treated with oligos directed against TGF-alpha, EGFR or their combination, respectively. We conclude that enhanced **bcl-2** expression followed **antisense** oligo induced growth factor deprivation. This result is similar to that found upon androgen deprivation therapy, and also demonstrates additional biologic activity of this new class of molecular therapeutic agents.

3/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10078364 97272124

Lck is necessary and sufficient for Fas-ligand expression and apoptotic cell death in mature cycling T cells.

Gonzalez-Garcia A; R-Borlado L; Leonardo E; Merida I; Martinez-A C; Carrera AC

Department of Immunology and Oncology, National Center of Biotechnology, Superior Council of Scientific Investigations, University Autonoma, Madrid, Spain.

Journal of immunology (UNITED STATES) May 1 **1997**, 158 (9) p4104-12, ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Apoptotic cell death is induced in mature cycling T cells upon ligation of the Ag-specific TCR. This process is essential for the maintenance of homeostasis in the immune system, as it is capable of down-regulating ongoing immune responses. The analysis of the mechanism underlying TCR-induced programmed cell death has focused the attention of many scientists recently. In this regard, several recent reports have implicated Fas/Fas-ligand molecules as the final mediators of this process. Several other gene products have been implicated in the control of apoptosis (as **Bcl-2** , p53, and c-Myc); however, no information was available in the early signaling molecules that trigger this phenomena. The results presented in this work indicate that pp56(lck) src family kinase is actually required for the TCR to trigger cell death in mature cycling T cells. In fact, while inhibition of pp56(lck) expression with **antisense** oligonucleotides blocked TCR-induced apoptosis, pharmacologic inhibition of phosphatidylinositol 3-kinase activity had no effect. Accordingly, ligation of the Ag receptor in a cell line defective for pp56(lck) expression was unable to induce apoptosis, although it induced cellular stimulation, as measured by the expression of CD69. In addition, we show in this work that expression of constitutively active pp56(lck) mutants, but not pp59(fyn) mutants, in the absence of any other TCR-derived signal, is sufficient to induce apoptosis not only in transformed, but also in normal cycling T cells. Finally, evidence is

presented indicating t[redacted] a mechanism through which p[redacted](lck) regulates TCR-induced apoptosis in mature cycling T cells is by controlling Fas-ligand expression.

3/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10072971 97151148
Interaction of an adenovirus 14.7-kilodalton protein inhibitor of tumor necrosis factor alpha cytolysis with a new member of the GTPase superfamily of signal transducers.
Li Y; Kang J; Horwitz MS
Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York 10461, USA.
Journal of virology (UNITED STATES) Feb **1997**, 71 (2) p1576-82, ISSN 0022-538X Journal Code: KCV
Contract/Grant No.: P30-CA13330, CA, NCI; 5T32 CA09060, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The adenovirus (Ad) 14.7-kDa E3 protein (E3-14.7K), which can inhibit tumor necrosis factor alpha (TNF-alpha) cytolysis, was used to screen HeLa cell cDNA libraries for interacting proteins in the yeast two-hybrid system. A new member of the low-molecular-weight (LMW) GTP-binding protein family with Ras and ADP-ribosylation factor homology was discovered by this selection and has been named FIP-1 (14.7K-interacting protein). FIP-1 colocalized with Ad E3-14.7K in the cytoplasm especially near the nuclear membrane and in discrete foci on or near the plasma membrane. Its interaction with E3-14.7K was dependent on the FIP-1 GTP-binding domain. The stable expression of FIP-1 **antisense** message partially protected the cells from TNF-alpha cytolysis. FIP-1 was associated transiently with several unknown phosphorylated cellular proteins within 15 min after treatment with TNF-alpha. FIP-1 mRNA was expressed ubiquitously but at higher levels in human skeletal muscle, heart, and brain. In addition to homology to other LMW GTP-binding proteins, FIP-1 has regions of homology to two prokaryotic metalloproteases. However, there was no homology between FIP-1 and any of the recently isolated death proteins in the TNF-alpha or Fas/APO1 cytolytic pathway and no interaction with several members of the **Bcl-2** family of inhibitors of apoptosis. These data suggest that FIP-1, as a cellular target for Ad E3-14.7K, is either a new intermediate on a previously described pathway or part of a novel TNF-alpha-induced cell death pathway. FIP-1 has two consensus sequences for myristoylation which would be expected to facilitate membrane association and also has sequences for Ser/Thr as well as Tyr phosphorylation that could affect its function.

3/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09958053 99238134
CD40 stimulation inhibits cell growth and Fas-mediated apoptosis in a thyroid cancer cell line.
Fujieda S; Sugimoto C; Seki M; Sunaga H; Saito H
Department of Otorhinolaryngology, Fukui Medical University, Yoshida, Japan. sfujieda@fmsrsa.fukui-med.ac.jp
Oncology research (UNITED STATES) **1998**, 10 (9) p433-9, ISSN 0965-0407 Journal Code: BBN
Languages: ENGLISH
Document type: JOURNAL ARTICLE
CD40 plays a critical role in the humoral immune response, especially in B-cell proliferation, differentiation, production of antibody, secretion of cytokines, and apoptosis. Here, we examined CD40 expression on six head and

neck cancer cell lines [redacted] flow cytometry. Only the HTC/[redacted] cell line, which originated from a thyroid cancer, expressed CD40 on the surface of the cells. Coculture with anti-CD40 mAb inhibited colony formation of HTC/C3 cells. CD40 stimulation enhanced Fas expression on HTC/C3 cells. Although HTC/C3 cells are sensitive to Fas-mediated apoptosis, CD40 stimulation inhibited Fas-mediated apoptosis in HTC/C3 cells. CD40 stimulation enhanced **Bcl-2** expression, and **antisense** oligonucleotide against **bcl-2** canceled the inhibition of HTC/C3 cell growth caused by CD40 stimulation. Additionally, more anti-CD40 mAb-treated HTC/C3 cells were accumulated in G1 phase, and fewer in S phase, compared to nontreated cells. These results suggest that CD40 stimulation might be involved in the slow growth rate of CD40-bearing cancer cells, and they suggest a new biological approach to the treatment of cancers.

3/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09879955 99218569
p53 mediates apoptosis induced by c-Myc activation in hypoxic or gamma irradiated fibroblasts [see comments]
Rupnow BA; Alarcon RM; Giaccia AJ; Knox SJ
Department of Radiation Oncology, Stanford University School of Medicine, Stanford, California 94305-5302, USA.
Cell death and differentiation (ENGLAND) Feb **1998**, 5 (2) p141-7, ISSN 1350-9047 Journal Code: C7U
Contract/Grant No.: CA68149-01, CA, NCI; CA64489-01, CA, NCI; CA67166-01, CA, NCI
Comment in Cell Death Differ 1998 Feb;5(2):129-31
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Deregulated c-Myc expression leads to a cellular state where proliferation and apoptosis are equally favored depending on the cellular microenvironment. Since the apoptotic sensitivity of many cells is influenced by the status of the p53 tumor suppressor gene, we investigated whether the induction of apoptosis by DNA damage or non-genotoxic stress are also influenced by the p53 status of cells with altered c-Myc activity. Rat-1 fibroblasts expressing a conditional c-Myc allele (c-MycER), were transfected to express an **antisense** RNA complimentary to p53 mRNA. Expression of **antisense** p53 RNA decreased p53 protein levels and delayed p53 accumulation following c-Myc activation. Under hypoxic or low serum conditions, cells expressing **antisense** p53 were substantially more resistant to c-Myc-induced apoptosis than were control cells. c-Myc activation also sensitized Rat-1 cells to radiation-induced apoptosis. Rat-1 cells expressing **antisense** p53 RNA were more resistant to apoptosis induced by the combined effects of c-Myc activation and gamma irradiation. In a similar manner, apoptosis induced by c-Myc in serum starved, hypoxic or gamma irradiated fibroblasts was also inhibited by **Bcl-2** . These data indicate that p53 is involved in c-Myc-mediated apoptosis under a variety of stresses which may influence tumor growth, evolution and response to therapy.

3/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09872154 99222077
Growth factors prevent changes in **Bcl-2** and Bax expression and neuronal apoptosis induced by nitric oxide.
Tamatani M; Ogawa S; Nunez G; Tohyama M
Department of Anatomy and Neuroscience, Osaka University Medical School, 2-2 Yamadaoka, Suita, Osaka 565, Japan. tama@anat2.med.osaka-u.ac.jp
Cell death and differentiation (ENGLAND) Oct **1998**, 5 (10) p911-9

, ISSN 1350-9047 Jour[redacted] Code: C7U
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Recent studies have shown that nitric oxide (NO) donors can trigger apoptosis of neurons, and growth factors such as insulin-like growth factor-1 (IGF-1) and basic fibroblast growth factor (bFGF) can protect against NO-induced neuronal cell death. The purpose of this study was to elucidate the possible mechanisms of NO-mediated neuronal apoptosis and the neuroprotective action of these growth factors. Both IGF-1 and bFGF prevented apoptosis induced by NO donors, sodium nitroprusside (SNP) or 3-morpholinosydnonimin (SIN-1) in hippocampal neuronal cultures. Incubation of neurons with SNP induced caspase-3-like activation following downregulation of **Bcl-2** and upregulation of Bax protein levels in cultured neurons. Treatment of neurons with a bax **antisense** oligonucleotide inhibited the caspase-3-like activation and neuronal death induced by SNP. In addition, treatment of neurons with an inhibitor of caspase-3, Ac-DEVD-CHO, together with SNP did not affect the changes in the protein levels, although it inhibited NO-induced cell death. Pretreatment of cultures with either IGF-1 or bFGF prior to NO exposure inhibited caspase-3-like activation together with the changes in **Bcl-2** and Bax protein levels. These results suggest that the changes in **Bcl-2** and Bax protein levels followed by caspase-3-like activation are a component in the cascade of NO-induced neuronal apoptosis, and that the neuroprotective actions of IGF-1 and bFGF might be due to inhibition of the changes in the protein levels of the **Bcl-2** family.

3/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09760450 99087416
Estrogen withdrawal-induced human breast cancer tumour regression in nude mice is prevented by **Bcl-2**.
Pratt MA; Krajewski S; Menard M; Krajewska M; Macleod H; Reed JC
Department of Pharmacology, University of Ottawa, Ont, Canada. cpratt@uottawa.ca
FEBS letters (NETHERLANDS) Dec 4 **1998**, 440 (3) p403-8, ISSN 0014-5793 Journal Code: EUH
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We recently showed that estrogen induces expression of the anti-apoptotic protein, **Bcl-2** in MCF-7 human breast cancer cells. Since estrogen-dependent breast tumours can regress following estrogen withdrawal, we hypothesized that stable **Bcl-2** expression would prevent estrogen-withdrawal induced regression of MCF-7 tumours. We therefore established tumours in ovariectomized female nude mice implanted with an estrogen-release pellet using untransfected MCF-7 cells or MCF-7 cells stably transfected with a **Bcl-2** cDNA sense or **antisense** expression vector. All tumours grew at similar rates indicating that **Bcl-2** levels have no effect on tumour formation. After removal of the estrogen pellet, **Bcl-2** **antisense** tumours and untransfected MCF-7 tumours regressed means of 49% and 52%, respectively, after estrogen pellet removal whereas **Bcl-2** sense tumours were significantly stabilized. Regressing tumours displayed characteristics of apoptotic cells. These results show that **Bcl-2** can prevent hormone-dependent breast tumour regression and are consistent with the notion that decreased **Bcl-2** levels following estrogen withdrawal renders hormone-dependent breast tumour cells sensitive to apoptotic regression.

3/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09720225 99054656

Modulation of apoptosis by endogenous Bcl-xL expression in MKN-45 human gastric cancer cells.

Kondo S; Shinomura Y; Kanayama S; Higashimoto Y; Kiyohara T; Zushi S; Kitamura S; Ueyama H; Matsuzawa Y

Second Department of Internal Medicine, Osaka University Medical School, Suita, Japan.

Oncogene (ENGLAND) Nov 19 **1998**, 17 (20) p2585-91, ISSN 0950-9232 Journal Code: ONC

Languages: ENGLISH

Document type: JOURNAL ARTICLE

This study was designed to clarify the role of endogenous Bcl-xL expression in modulating apoptosis of malignant cells. Administration of bcl-x-**antisense** oligonucleotides decreased Bcl-xL protein levels in the MKN-45 human gastric cancer cell line. The decrease in Bcl-xL protein content resulted in increased cell death induced by serum deprivation or Fas-antibody administration. Flow cytometric analysis revealed that the increased apoptotic cell death was more prominent in bcl-x-**antisense** -treated cells as compared to control cells, bcl-x-sense-treated cells, or bcl-x-nonsense-treated cells. To inhibit the effect of intrinsic Bcl-xL protein, we overexpressed Bak, which binds Bcl-xL and inhibits the anti-apoptotic effect of Bcl-xL, by transfection into MKN-45 cells. Bak-overexpressing cells showed increased apoptotic cell death induced by Fas-antibody when compared to parent cells and MKN-neo-transfected cells. Bak-overexpressing cells also showed greater sensitization to 5-fluorouracil and cisplatin than parent cells and MKN-neo-transfected cells. In conclusion, we demonstrated that administration of bcl-x-**antisense** oligonucleotides or overexpression of Bak protein induces sensitization to apoptosis in MKN-45 gastric cancer cells, suggesting that endogenous Bcl-xL expression in cancer cells is an important modulator of apoptosis.

3/3,AB/16 (Item 16 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

09716072 99019739

Caspase-2 (Nedd-2) processing and death of trophic factor-deprived PC12 cells and sympathetic neurons occur independently of caspase-3 (CPP32)-like activity.

Stefanis L; Troy CM; Qi H; Shelanski ML; Greene LA

Department of Pathology, Taub Center for Alzheimer's Disease Research and Center for Neurobiology and Behavior, Columbia University College of Physicians and Surgeons, New York, New York 10032, USA.

Journal of neuroscience (UNITED STATES) Nov 15 **1998**, 18 (22) p9204-15, ISSN 0270-6474 Journal Code: JDF

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We have previously shown that caspase-2 (Nedd-2) is required for apoptosis induced by withdrawal of trophic support from PC12 cells and sympathetic neurons. Here, we examine the relationship of caspase-2 processing and cell death to induction of caspase-3 (CPP32)-like activity in PC12 cells. Caspase-2 processing, at a site tentatively identified as D333, led to the formation of an N-terminal 37 kDa product. This processing correlated temporally with induction of caspase-3-like activity. Agents previously shown to inhibit caspase-3-like activation, such as **bcl-2** and the Cdk inhibitor flavopiridol, also acted upstream of caspase-2 processing. The general caspase inhibitors BAF and zVAD-FMK inhibited N-terminal caspase-2 processing. In contrast, the more selective caspase inhibitor DEVD-FMK inhibited the induction of caspase-3-like activity but did not affect caspase-2 processing or significantly suppress death in PC12 cells or sympathetic neurons. This indicates that